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Supplementary oxygen during exercise training in COPD - full of hot air?

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Long term oxygen therapy is widely accepted as a treatment for severe hypoxaemia in patients with chronic respiratory disorders, based on survival findings from the UK Medical Research Council study[1] and the US Nocturnal Oxygen Therapy Trial[2]. The data from these landmark studies have driven the underlying rationale that correcting hypoxaemia is beneficial, and have led to the prescription of oxygen for other indications, including ambulatory oxygen for patients with exercise-induced oxygen desaturation (EID), nocturnal oxygen therapy for patients with nocturnal hypoxaemia and short burst oxygen for palliation of dyspnoea. This is despite a lack of supporting evidence from randomized clinical trials to support these indications[3-5].

A clinical indication that stimulates long-standing debate is the specific use of supplemental oxygen during exercise training in patients with EID. There is a sound physiological rationale in that supplemental oxygen can reduce respiratory rate and dynamic hyperinflation[6]. It also improves oxygen delivery, leading to a reduction in exercise-associated metabolic acidosis [7]. More than sixty years ago, Cotes and colleagues demonstrated that ambulatory oxygen could support outpatients with chronic respiratory insufficiency during exercise by improving arterial oxygen saturation and increasing walking time[8]. Subsequent, largely laboratory-based, studies have demonstrated a positive, albeit heterogeneous, benefit in exercise time following acute administration of oxygen during an exercise test in patients with COPD or cystic fibrosis[9, 10]. This had led to the logical hypothesis that by improving exercise time acutely, supplemental oxygen allows patients to tolerate training sessions of higher intensity with consequently gain greater benefit from an exercise training programme.

Although there have been attempts to provide evidence to support this hypothesis [11-14], the results from clinical trials have been mixed and inconclusive, largely due to methodological issues, small sample sizes and inclusion of a heterogeneous population, including existing long-term oxygen users [11] or individuals without EID [13, 14].

In this issue of the *European Respiratory Journal*, Alison and colleagues report on a double-blind randomised placebo-controlled trial that aimed to determine whether supplemental oxygen administered during exercise training was more effective than medical air in improving endurance exercise capacity; health-related quality of life; peak walking capacity; dyspnoea and physical activity levels in patients with COPD who were normoxaemic at rest but desaturated during exercise (<90% during the six-minute walk test)[15]. Following random allocation to either oxygen or compressed air, both groups underwent an eight-week training programme with three supervised exercise sessions per week. Training initially consisted of 30 minutes of individualised aerobic exercise (20 minutes of treadmill walking and 10 minutes of stationary cycling). Training intensity was increased according to target dyspnoea scores (3-4 on modified dyspnoea scale [16]) and training duration was increased according to a fixed protocol. The results of this study demonstrated that both groups improved exercise capacity and health-related quality of life following exercise training, but no added benefit was seen with supplemental oxygen in either of the primary outcomes measures of endurance shuttle walk test and chronic respiratory questionnaire, nor in any of the secondary outcome measures. This was a well-designed and conducted study, with clear eligibility criteria, high retention of participants, and successful blinding of participants, trainers and assessors: a feature absent in previous trials[11-14].

A fundamental observation was that the oxygen group were not able to achieve a greater training dose per session than the compressed air group, despite a significantly higher measured oxygen saturation and significantly lower dyspnoea and perceived exertion scores during treadmill training sessions. Without an increased training load, it was not altogether surprising that no between-group differences in response to exercise-training were observed. The authors speculated that the large physiological stimulus applied to both groups overwhelmed the small physiological advantage of acute oxygen administration. Although this is a highly plausible explanation (observed in previous pulmonary rehabilitation adjunct trials[17, 18]), other mechanisms may have limited exercise-training load. The authors did not provide data regarding leg effort or lower limb symptoms, which are reported frequently as a reason for terminating exercise in a proportion of patients with COPD[19]. The exercise-training programme was protocolized such that exercise type and frequency were fixed and exercise duration was progressed up to a maximum of 40 minutes by week three. From this point onwards, staff supervising exercise-training could only increase training intensity (speed of treadmill and cycle workload) but not duration of training – the parameter that is most consistently influenced by acute oxygen response studies. Another speculative explanation is that because the trainers were blinded to treatment allocation and to patients' oxygen saturation during training, they may have inadvertently been more cautious of increasing training intensity in patients known to desaturate during exercise (of whom half were using air). Circumstantial evidence to support this is the observation that the responses to exercise-training in both groups, although statistically significant, were smaller than expected and did not achieve the minimum clinically important difference of the incremental shuttle walk test nor some domains of the Chronic Respiratory Questionnaire following the exercise-training programme.

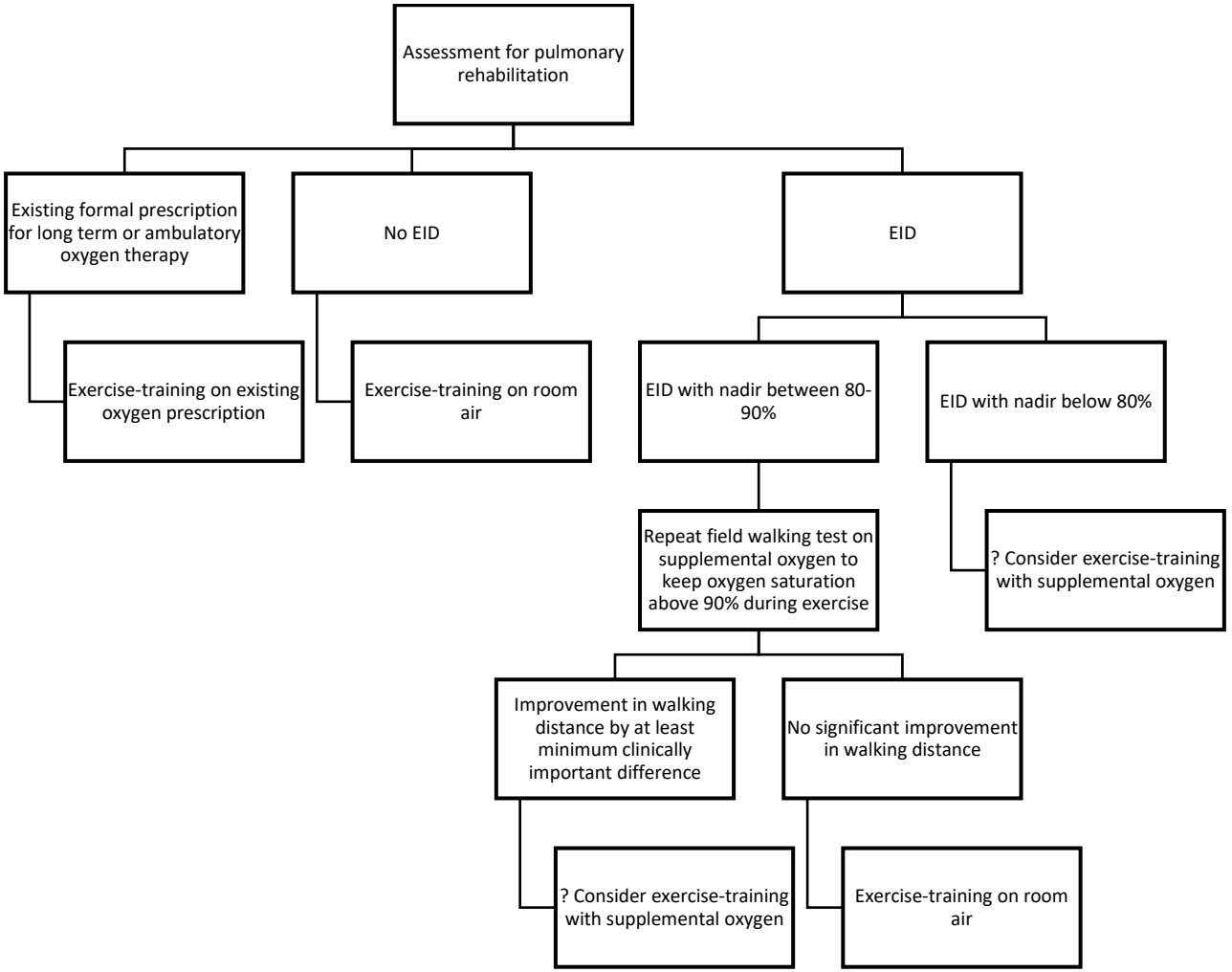
Another important consideration is that most participants had moderate EID, and the trial was therefore underpowered to detect an effect of supplemental oxygen in patients with more severe EID (nadir below 80%). Furthermore, prior to the start of the exercise programme, the acute physiological response to oxygen was not tested, hence it is not clear as to the proportion of acute oxygen responders and non-responders in the treatment and control groups. Hence the results of the trial cannot be extrapolated to the specific subgroups of patients with COPD and severe EID, those who have shown a beneficial response to acute oxygen administration, nor patients with non-COPD disorders (such as idiopathic pulmonary fibrosis and pulmonary hypertension) and EID. Further research is required to understand the role of supplemental oxygen in the exercise-training of these patient subgroups.

Alison and colleagues should be congratulated in rigorously conducting the largest study to date to examine the role of supplemental oxygen during exercise-training in patients with COPD and EID. They provide convincing data that the majority of patients with COPD and EID safely benefit from exercise-training without the need for supplemental oxygen. This supports the recommendations of international pulmonary rehabilitation guidelines that supplemental oxygen should not be routinely prescribed in patients with COPD who desaturate but do not fulfil indications for long-term oxygen therapy [20-22]. The findings therefore may help to simplify the assessment process of patients with EID for exercise-training interventions such as pulmonary rehabilitation. We present our current assessment algorithm prior to commencement of pulmonary rehabilitation (Figure 1), which acknowledges remaining uncertainty around the role of supplemental oxygen in specific patient subgroups, namely those who show an acute response to supplemental oxygen and those with severe EID.

Although Alison and colleagues intended to explore whether exercise-training or pulmonary rehabilitation in patients with EID could be enhanced with supplemental oxygen, perhaps the most important clinical implication of this study is that for the vast majority of patients, the non-availability of supplemental oxygen need not be a barrier to using community and non-medical settings to deliver pulmonary rehabilitation. This potentially increases the accessibility, utilization and reach of an evidence-based intervention that is considerably more effective in reducing symptom burden in COPD than supplemental oxygen alone.

Figure Legend

Figure 1: An algorithm to assessing exercise induced oxygen desaturation (EID) (defined as nadir oxygen saturation below 90% during a field walking test performed on room air) in patients with COPD referred for pulmonary rehabilitation.


Assessment for pulmonary rehabilitation
Existing formal prescription for long term or ambulatory oxygen therapy
No EID
EID
Exercise-training on existing oxygen prescription
Exercise-training on room air
EID with nadir between 80-90%
EID with nadir below 80%
Repeat field walking test on supplemental oxygen to keep oxygen saturation above 90% during exercise
? Consider exercise-training with supplemental oxygen
Improvement in walking distance by at least minimum clinically important difference
No significant improvement in walking distance
? Consider exercise-training with supplemental oxygen
Exercise-training on room air

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